



Neuroscience Module

Lecture (3)

Ammonia metabolism

By

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Biochemistry and Molecular
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Lecture Key points



- Ammonia toxicity, transport and detoxification through urea cycle

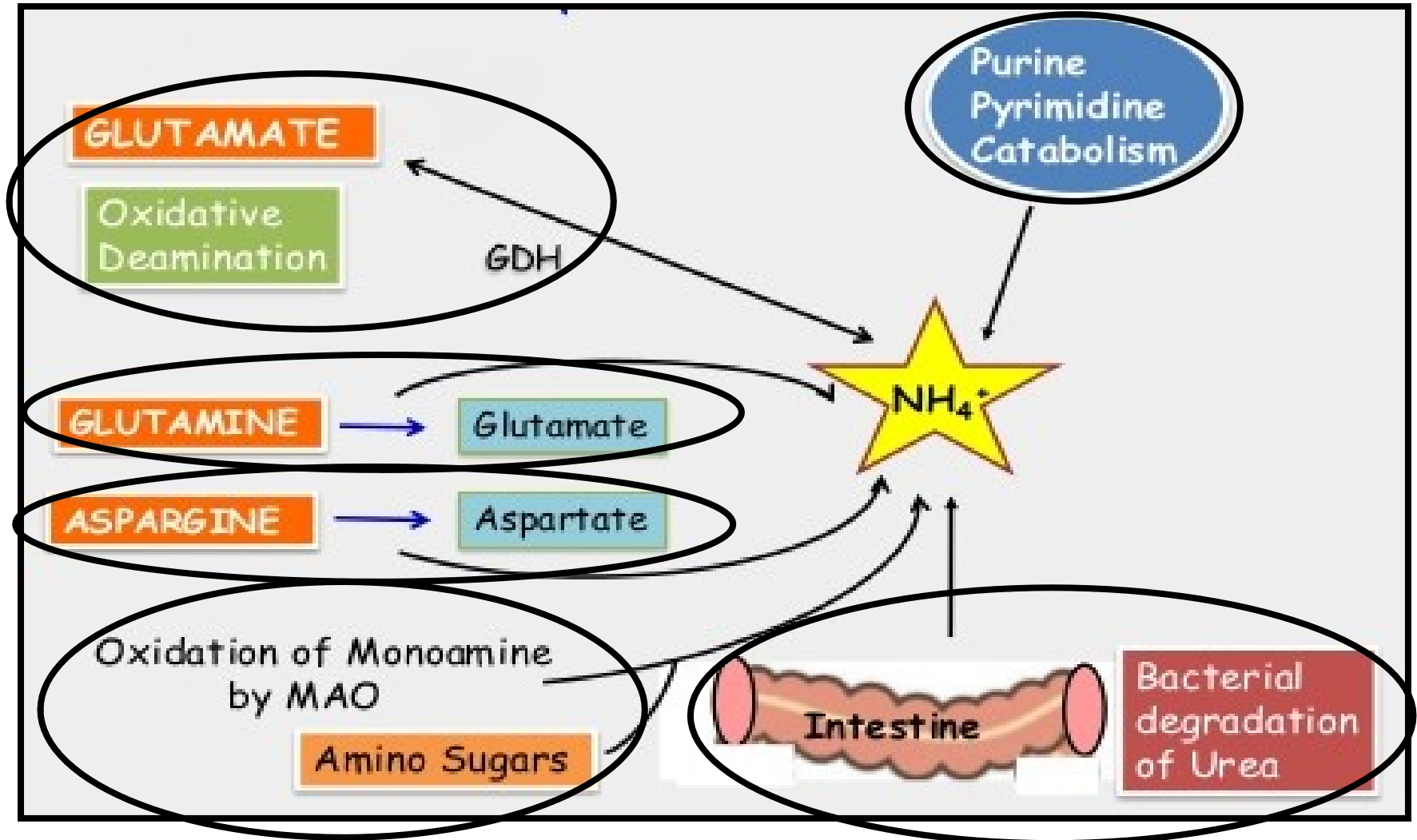
INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

1. Justify the causes of ammonia toxicity
2. Outline the transport of ammonia in the blood
3. Illustrate the reactions of urea cycle

Sources and fate of ammonia

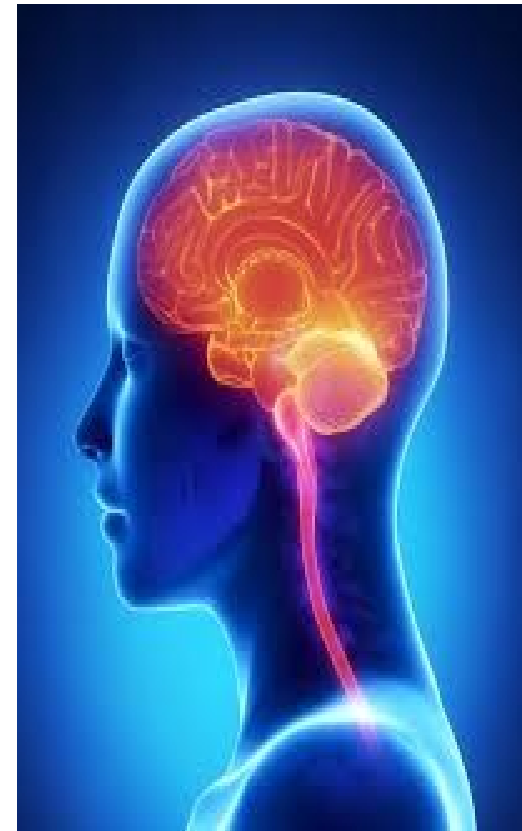




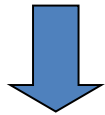
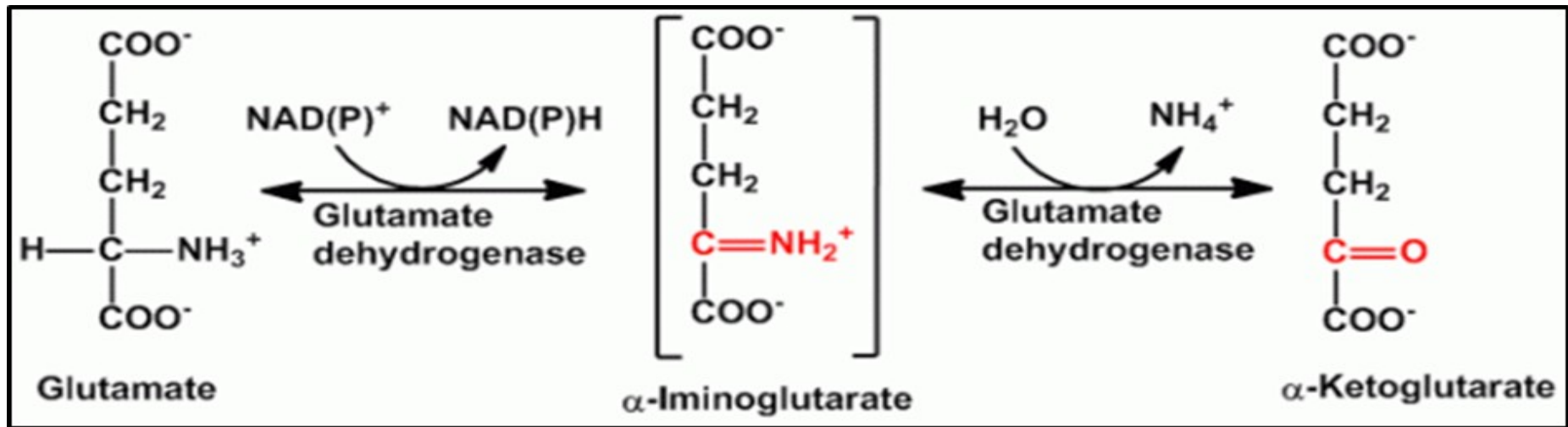
STOP



Ammonia.



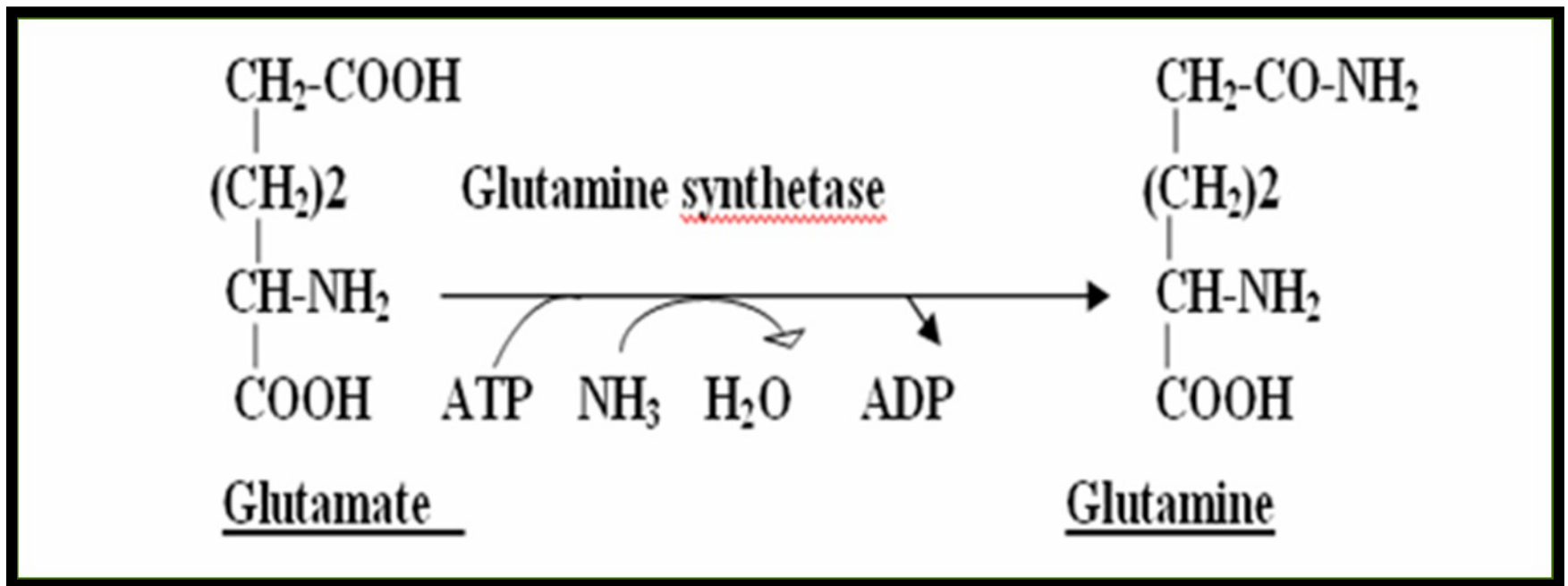
1) The level of α -KG is reduced



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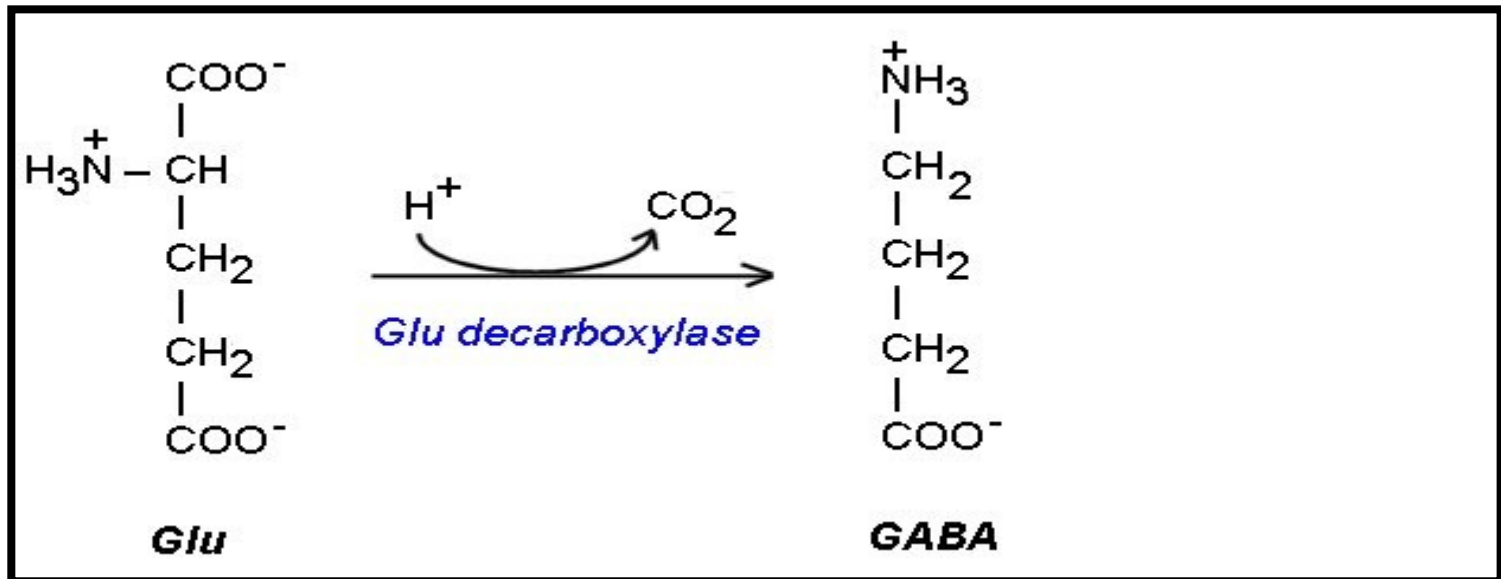
- **shortage in TCA-cycle**
- **and \downarrow ATP generation which is**
- **required for various brain activities**

2) Depletion of **glutamate** in brain (to form **glutamine**)



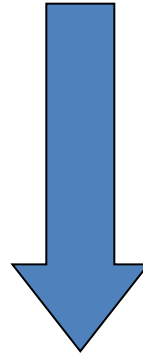
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2) Depletion of **glutamate** in brain decreases production of **GABA**



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3) **Elevated** levels increases the **permeability to K^+ and Cl^-** ions to the brain.



- **Interference with electrical activity of the brain**

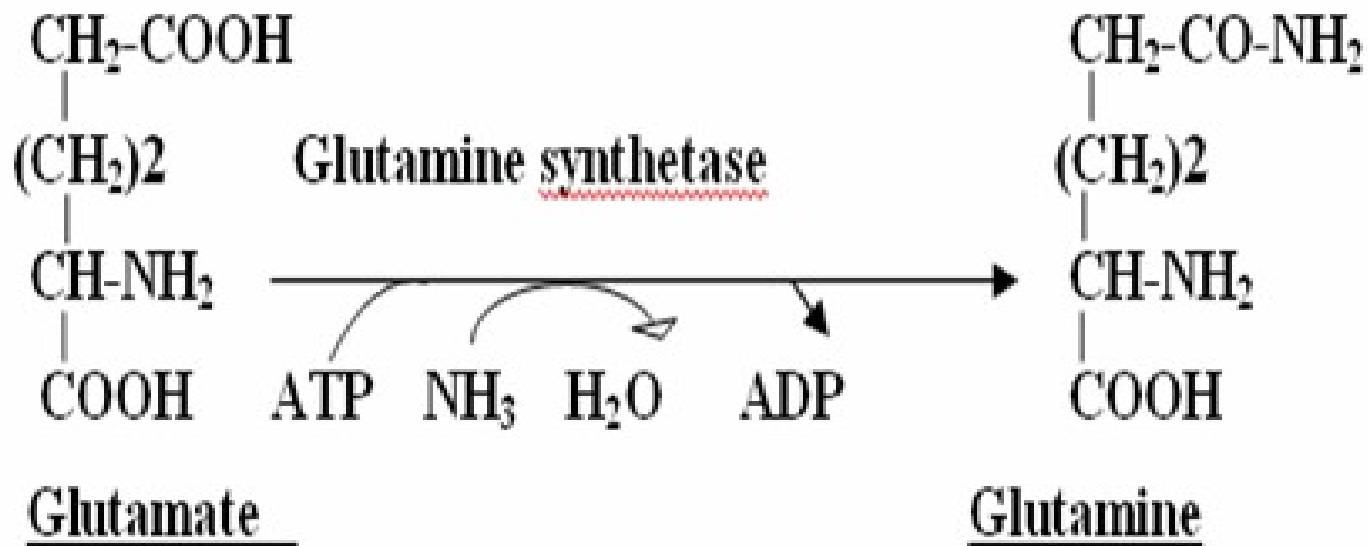
- 4) Excess glutamine is exchanged with Tryptophan a precursor for serotonin (Excitatory neurotransmitter).
- 5) Glutamine causes osmotic shift of water into cells resulting in cerebral edema.

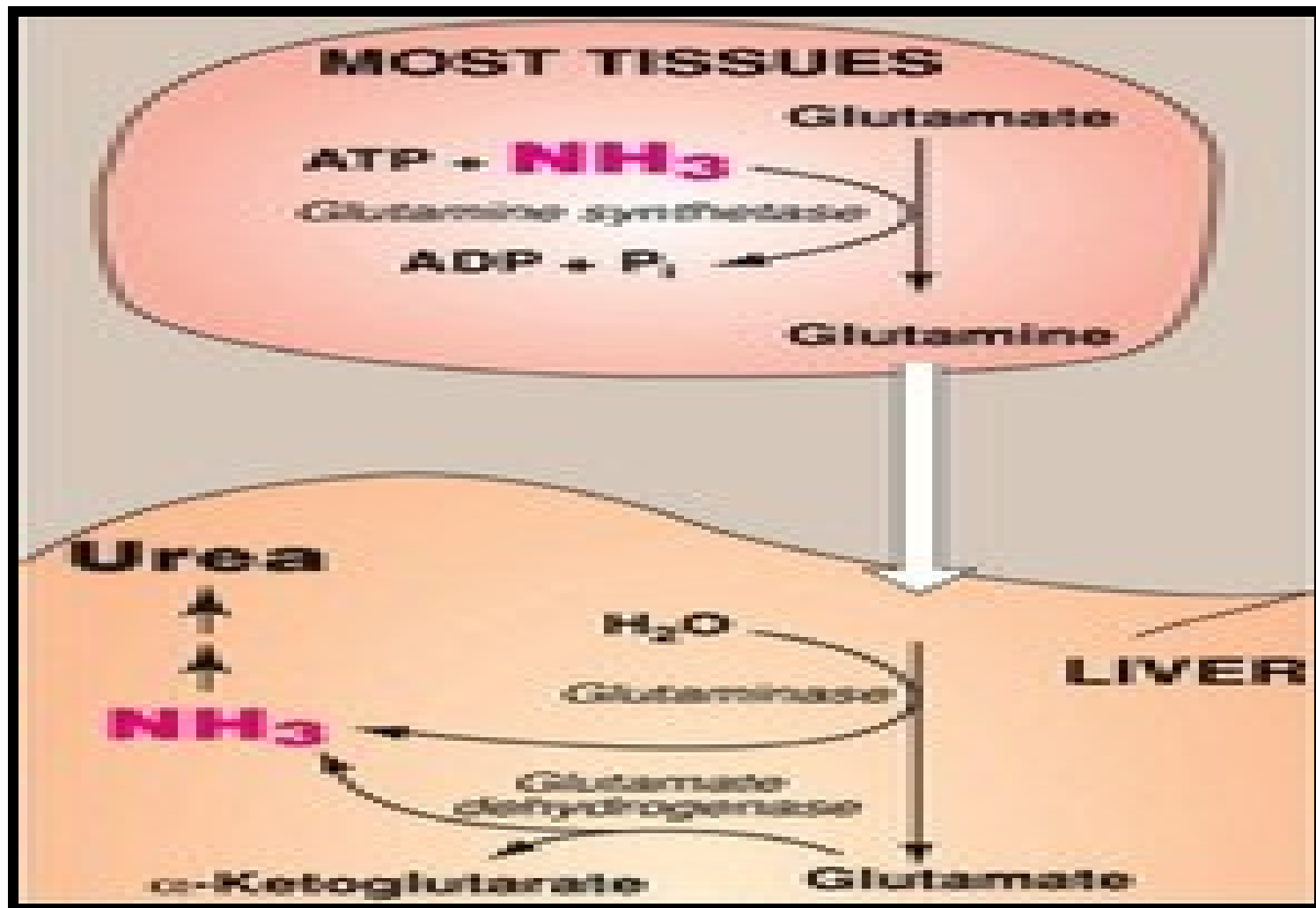
Ammonia Transport

1) Ammonium ion (NH_4^+)

2) Ammonia Transport in the form of glutamine

- Glutamine synthetase (mitochondrial enzyme) fixes ammonia as glutamine.



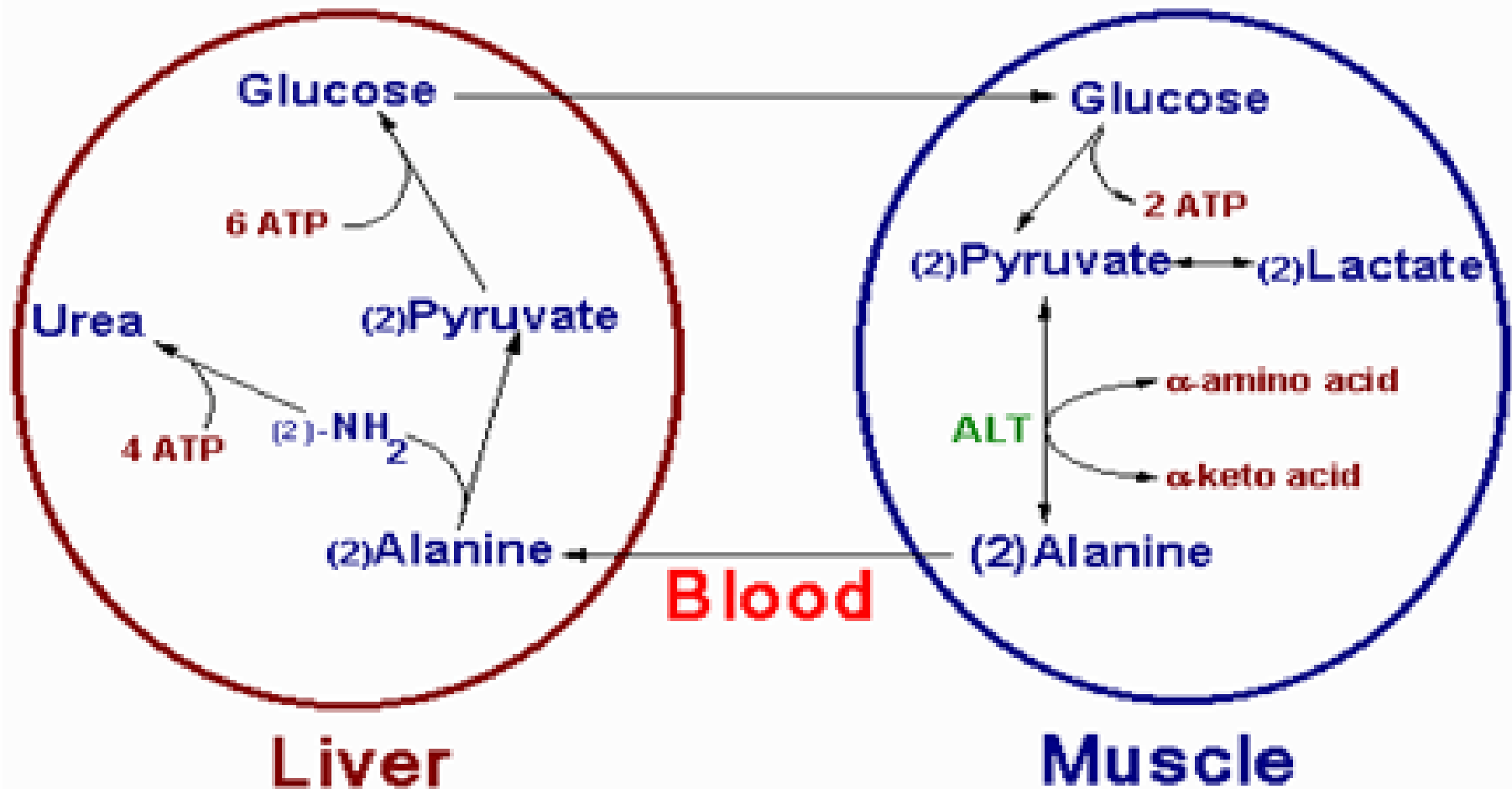


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Neuroscience module

3) Ammonia Transport in the form of Alanine

Muscle sends nitrogen to the liver as alanine in addition to glutamine

Glucose/Alanine Cycle



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Ammonia toxicity, transport and detoxification through urea cycle (Quiz)



Ammonia is toxic to the brain. Justify

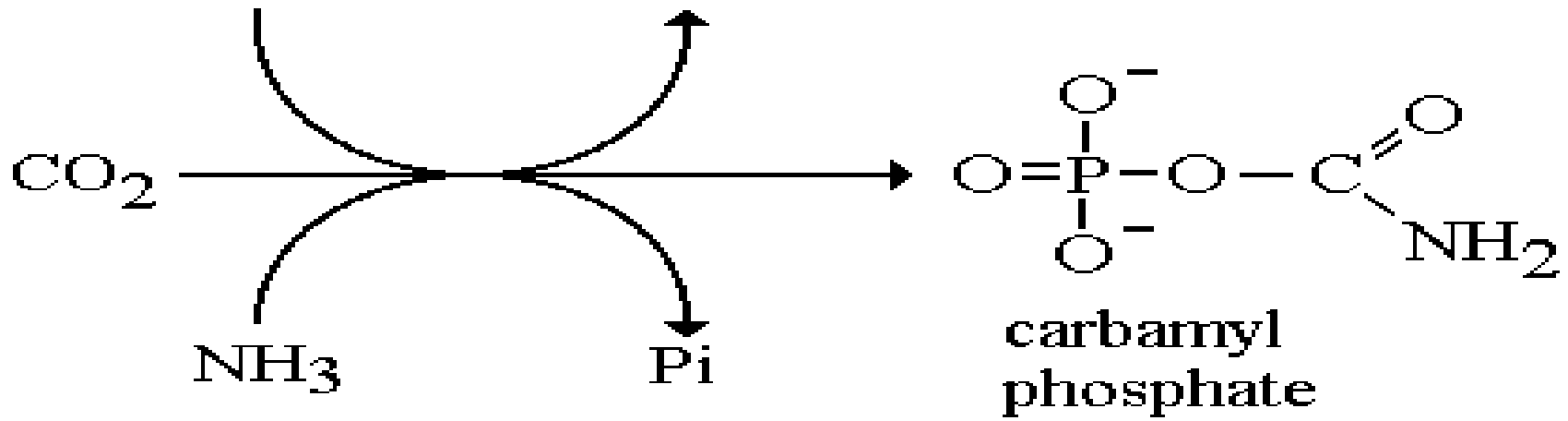
Urea cycle

-Synthesis of urea occurs in the liver in 5 reactions.

-The first 2 reactions proceed in mitochondria of liver cells.

-while the remaining 3 proceed in cytosol of liver cells.

1) Biosynthesis of carbamoyl phosphate



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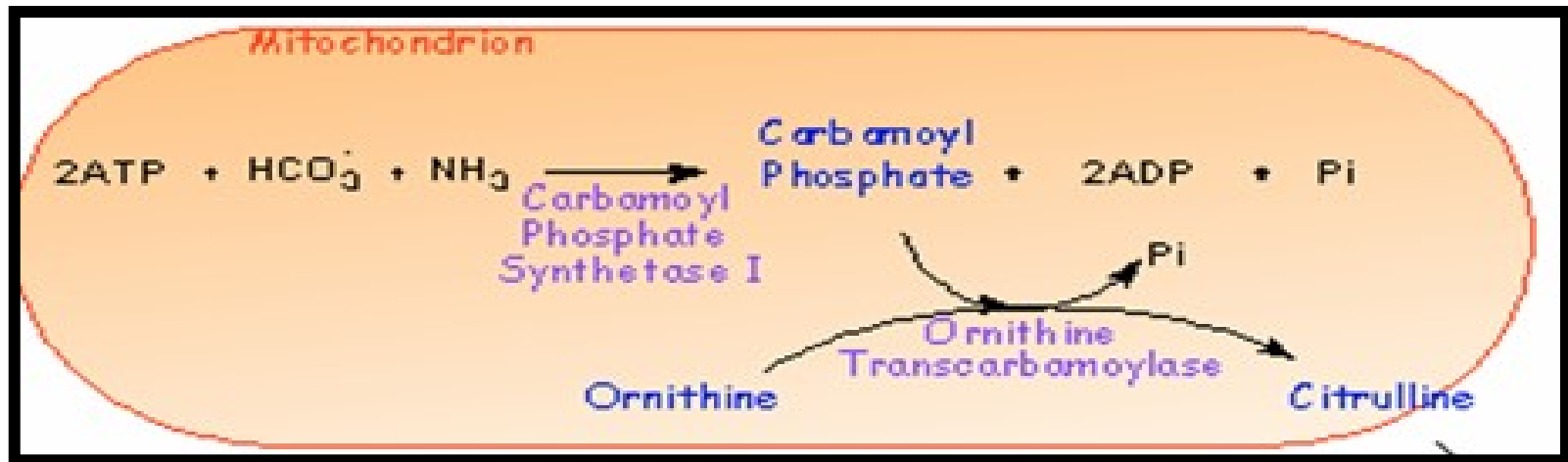
energy

(CO_2 is a product of citric acid cycle, ammonia is derived from glutamate by deamination, the phosphate and energy are derived from ATP).

- It is catalyzed by **mitochondrial carbamoyl phosphate synthetase I (CPS I)** (the rate-limiting enzyme of urea cycle).

- **2 ATPs** are required

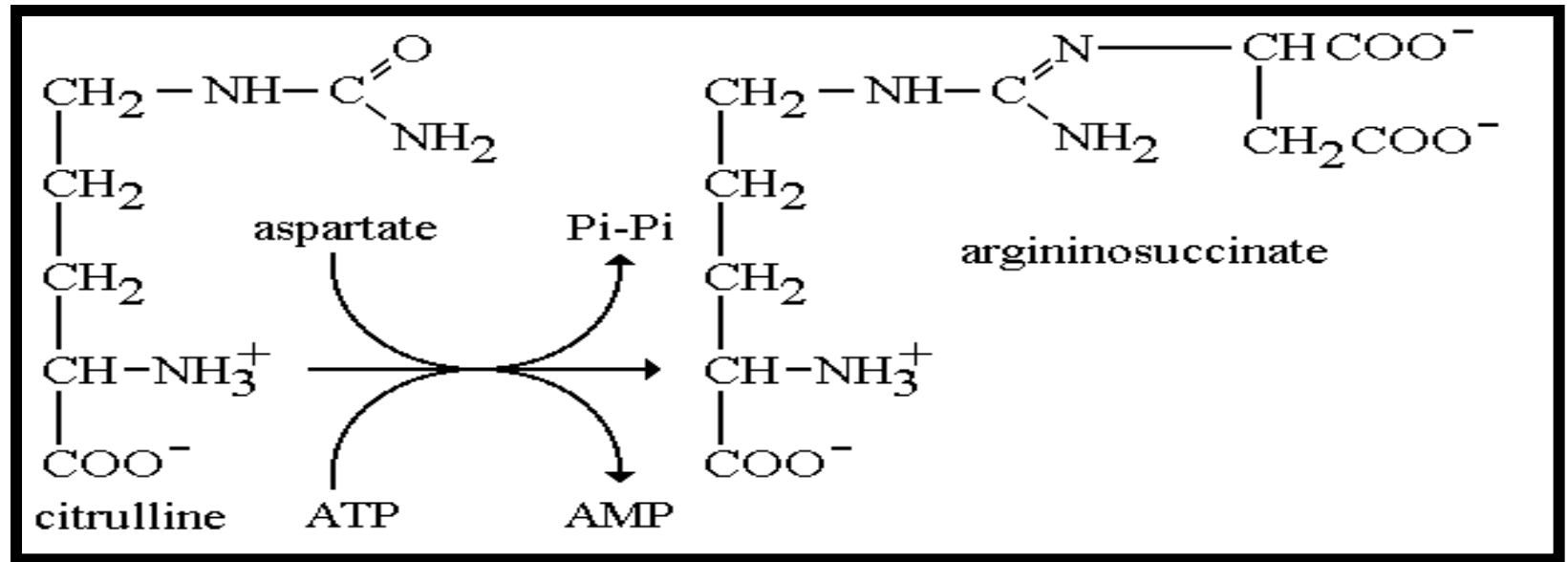
2- Formation of citrulline



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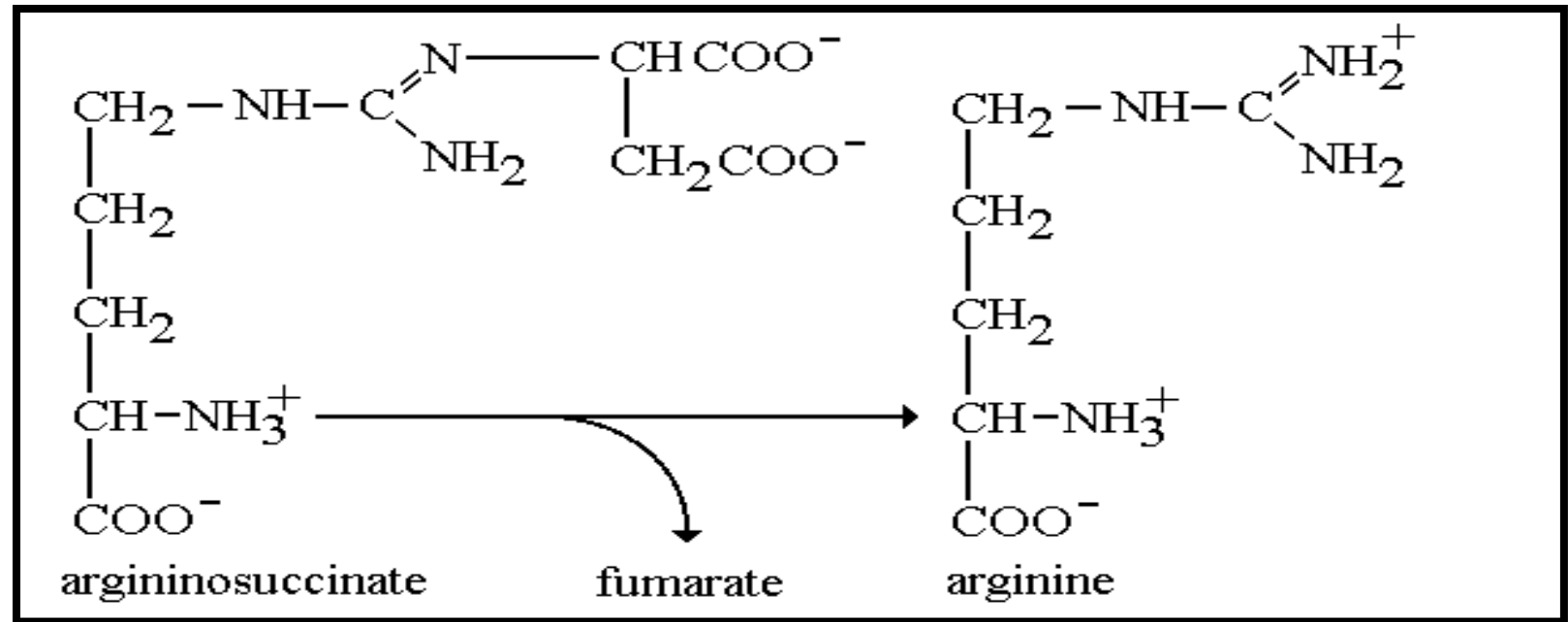
The carbamoyl portion of carbamoyl phosphate is transferred to ornithine by **ornithine transcarbamoylase (OTC)** and the high-energy phosphate is released as inorganic phosphate. The reaction product, citrulline, is transported to the cytosol.

3- Formation of argininosuccinate



- One molecule of **aspartic acid** is added to citrulline forming **argininosuccinate** which provides the **2nd** N of urea.
- Catalyzed by argininosuccinate synthetase

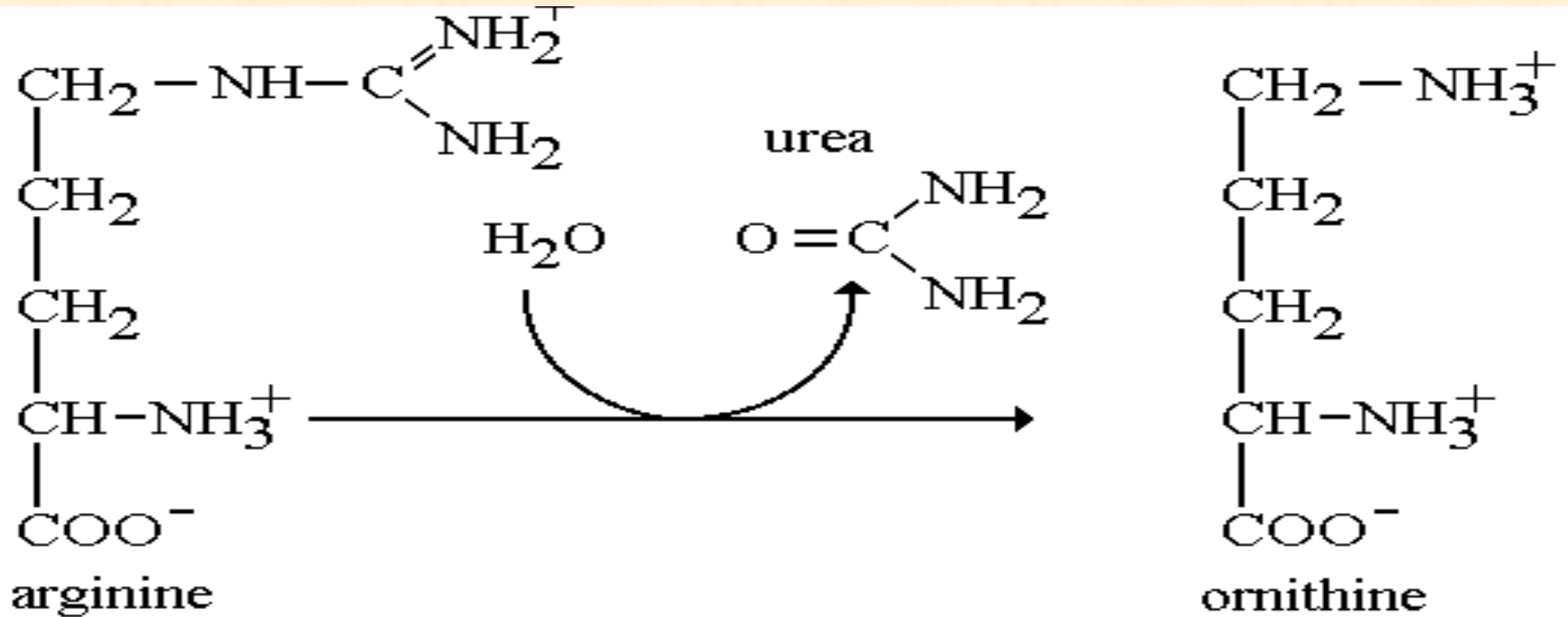
4- Cleavage of argininosuccinate



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Argininosuccinate is cleaved by
argininosuccinate
lyase to yield arginine and fumarate

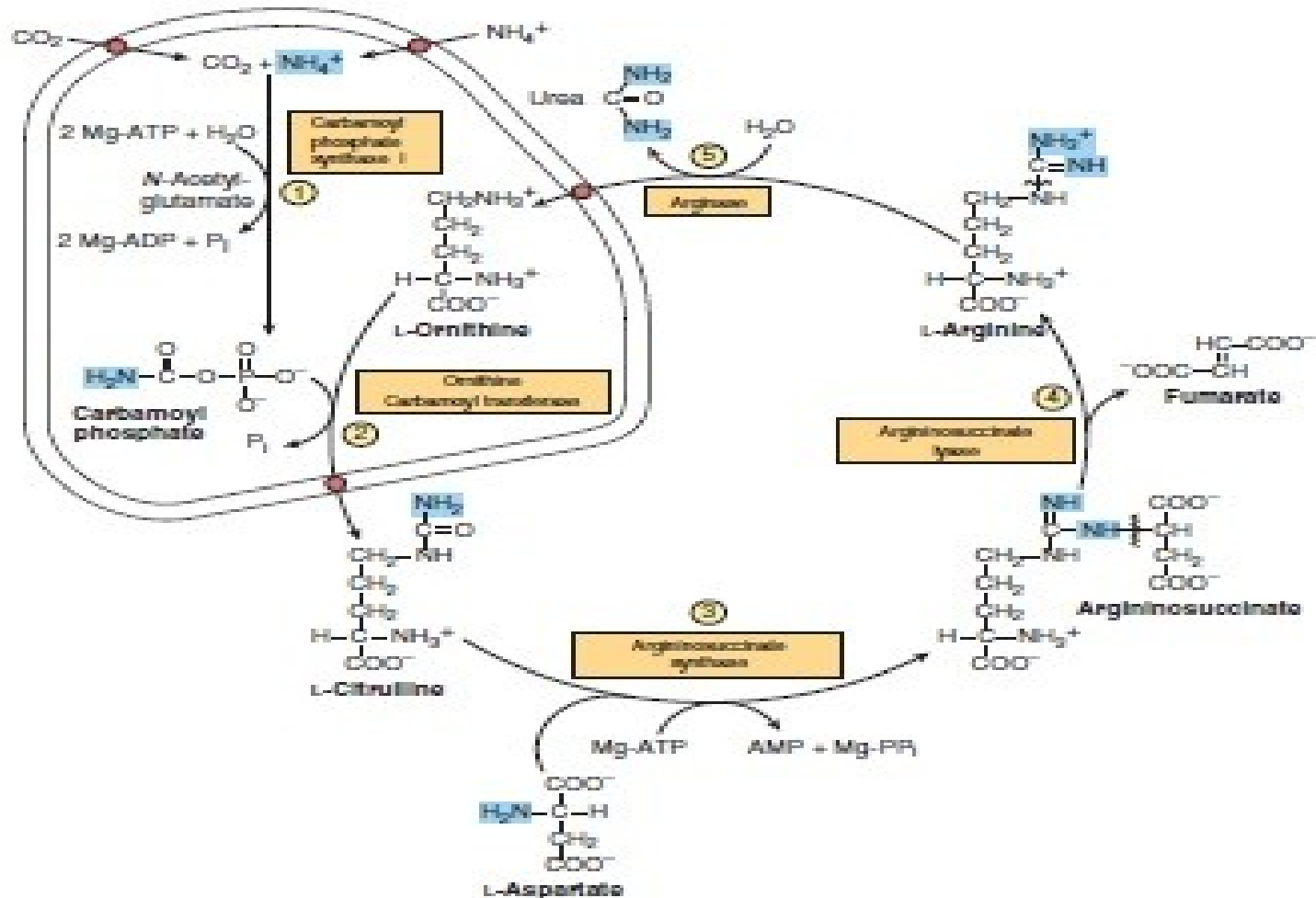
5- Cleavage of arginine by arginase into urea and ornithine



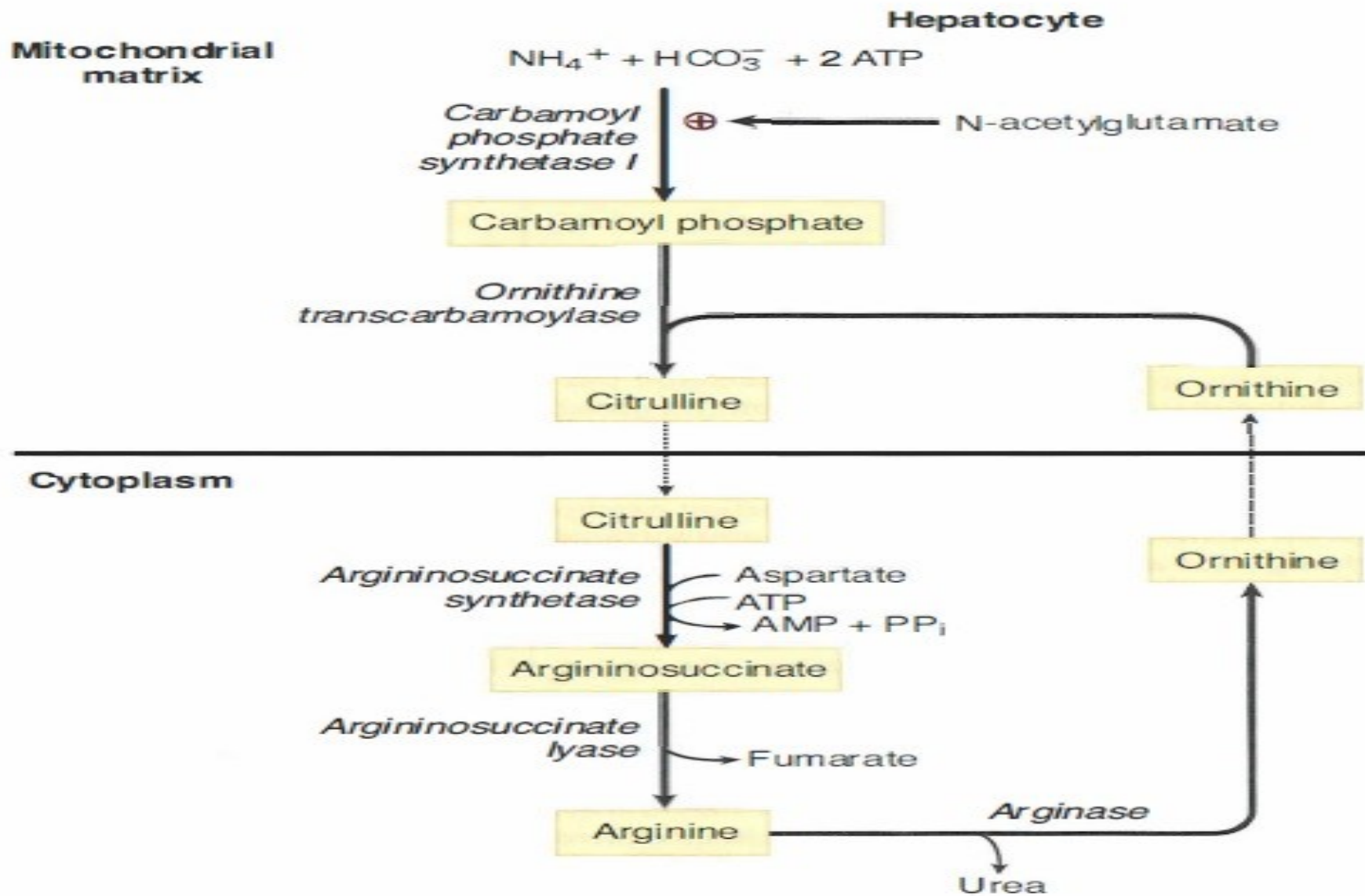
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N.B Ornithine and citrulline are basic amino acids that participate in the urea cycle, moving across the inner mitochondrial membrane via a cotransporter.

Urea cycle



Urea cycle

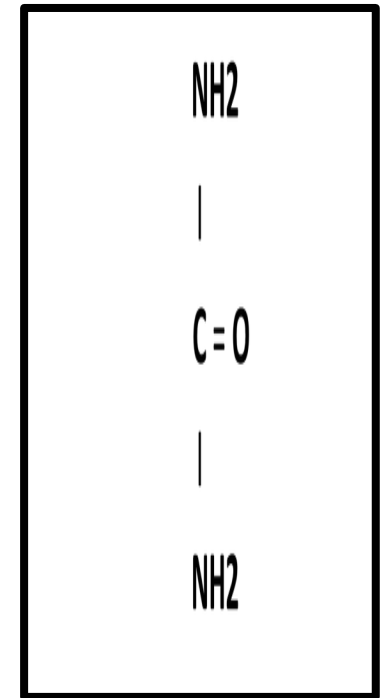


Sources of urea nitrogen

Urea contains 2 nitrogen atoms:

1) The first arises from ammonia.

2) The second arises in cytosol from aspartate



Source of carbon

CO₂

Urea Formation:

Although the urea formation requires the participation of **3 ATP molecules, yet it consumes **4 ATP** from the energetic point of view as 4 high energy phosphate bonds are hydrolyzed” recall that conversion of ATP to AMP release **PPi**”.**

Ammonia toxicity, transport and detoxification through urea cycle (Quiz)

In patients with liver cell failure, the following is NOT elevated in blood:

- (A) Ammonia
- (B) Glutamine
- (C) Alanine
- (D) Urea

Summary

- Hyperammonemia, has toxic effects in the brain (cerebral edema, convulsions, coma, and death).
- Most excess nitrogen is converted to urea in the liver and goes through the blood to the kidney, where it is eliminated in urine.

SUGGESTED TEXTBOOKS



- Lippincott's illustrated reviews in Biochemistry by P.C. Champe, R.A. Harvey and D.R. Ferrier
- Fundamentals of Clinical Chemistry (Tietz)
- "Textbook of Biochemistry with Clinical Correlations" by T.M. Devlin
- "Harper's Biochemistry" by R.K. Murray, D.K. Granner, P.A. Mayes and V.W. Rodwell

A close-up photograph of a bouquet of red roses. The roses are in various stages of bloom, with some showing deep red petals and others more tightly curled. Green leaves are interspersed among the flowers. A white rectangular box with a thin black border is centered over the middle of the bouquet, containing the text "THANK YOU" in bold, orange, sans-serif capital letters.

THANK YOU